REMARKS

After entry of this amendment, claims 1, 3-20, and 22-37 are pending. Claims 1, 3, 20, and 22 are amended to expedite prosecution. Amendments to claims 3 and 22 are supported, for example, in the specification on page 20, lines 6-7. New claims 35-37 are supported, for example, in the specification on page 16, line 27 to page 17, line 7.

35 U.S.C. § 112 Rejections

Reconsideration is respectfully requested of the rejection of claims 1, 3-20, and 22-34 as failing to satisfy the enablement requirement of 35 U.S.C. § 112. As explained in the prior responses, applicant respectfully maintains that the pending claims are fully enabled. However, to expedite prosecution, the claims have been amended to recite methods for reducing mucositis in patients exposed to radiation or anti-tumor platinum-coordination compounds by administration of a protectant agent comprising methionine. Dependent claims 4, 5, and 6 recite D-methionine, L-methionine, or DL-methionine as the protective agent. The Office asserts that "the quantity of experiment[ation] will be undue as one has to conduct test[s] on [a] series of methionine-like compounds to screen which of these methionine-like compounds will reduce mucositis."[1] However, the amended claims encompass only the D-, and L- isomers and the racemic mixture of methionine and are enabled because the experimentation required to test for each agent's protectant efficacy against mucositis is narrowly limited, and certainly not undue.

Even less experimentation would be needed for the method of new dependent claims 35, 36, and 37, which are directed to oral mucositis, esophageal mucositis, and gastrointestinal mucositis, respectively. Applicant has previously presented evidence regarding methionine's effectiveness for oral mucositis and a person of ordinary skill would have appreciated from applicant's disclosure that methionine protectant agents would have been effective for treating esophageal and gastrointestinal mucositis as well.

Independent claims 33 and 34 recite S-adenosyl-L-methionine as the protective agent. Similar to claims 1, 3-20, and 22-32, these claims are enabled because the experimentation

[1] See Office action dated November 7, 2006 at pages 5-6.

required to test for each agent's protectant efficacy against mucositis is so narrowly limited that it would not have been undue. Thus, claims 1, 3-20, and 22-37 satisfy the enablement requirement of 35 U.S.C. § 112.

35 U.S.C. § 103 Rejection

Reconsideration is respectfully requested of the rejection of claims 1, 3-15, 22-28, and 33-34 as unpatentable over U.S. Patent No. 6,265,386 (Campbell) in view of U.S. Patent No. 4,961,926 (Gabrilove). The Office asserts that "[i]t is well known in the art of cancer or chemotherapy to protect the mucosal track prior to administering either the chemotherapy or the radiation"[2] and that whether explicitly "recited by the cited reference or not, the skilled artisan would have been motivated to administer the drug."[2] However, it is respectfully noted that the Campbell patent makes no mention of mucositis resulting from any type of insult; and that the patent contains not the remotest suggestion that methionine or methionine-like moieties would have any value in dealing with mucositis resulting from radiation exposure or administration of an anti-tumor platinum-coordination compound.

Gabrilove discloses methods of preventing mucositis comprising administering granulocyte colony stimulating factor (GCSF) or a polypeptide analog thereof. In particular, the GCSF analog may be a nonglycosylated polypeptide having an amino acid sequence identical to the sequence of the polypeptide component of naturally occurring GCSF (GCSF contains at least 144 amino acids) except for the presence of an additional methionine at the N-terminus. In one embodiment described in the Gabrilove reference, this 20,000 Dalton protein has one additional methionine residue to give a total of 145 amino acids. In contrast, methionine is small molecule of approximately 150 Daltons. Claims 1 and 20 require administration of a protectant agent comprising monomeric methionine and claims 33 and 34 require administration of another small molecule protectant agent comprising 2-adenosyl methionine.

It is respectfully submitted that there is no basis in the record for combining Gabrilove with Campbell for any purpose. Moreover, even if by hindsight Campbell was brought together

[2] See Office action dated November 7, 2006 at page 4.

with Gabrilove, the combination would not have led a person of ordinary skill to find the present claims for reducing mucositis using the small molecule methionine obvious without resorting to further impermissible hindsight using applicant's disclosure as a template. A skilled person would have attributed the anti-mucositis effect of the GCSF protein to the specific structural aspects of the protein and not solely or primarily to the presence of an additional methionine residue at the N-terminus. From the Gabrilove disclosure, a skilled person would have learned that recombinant hG-SCF (rhG-CSF) is "a specific growth and differentiation factor for neutrophil granulocytes"[3] and that "recombinant hG-SCF may reduce the incidence of mucositis by enhancing the number of neutrophils, as well as their functional capability to guard the mucosal barriers more efficiently"[4]. From these statements, a skilled person would have known that the primary, secondary, and tertiary structure of the 20,000 Dalton rhG-CSF protein was instrumental in its neutrophil granulocyte growth stimulation and mucositis protection functions.

A skilled person would not have expected monomeric methionine, a 150 Dalton small molecule, to provide the same physiological effect as the 20,000 Dalton GSCF protein, regardless of whether having an additional methionine unit happens to be present at the protein N-terminus. Even if it were assumed that an additional methionine at the N-terminus of the GSCF protein is somehow instrumental in imparting significant properties to the protein as a whole, one skilled in the art would scarcely expect that the monomeric amino acid by itself would provide a comparable effect. By way of example, proteins, including GSCF proteins act upon cell components through various chemical and physical interactions. In particular, the primary, secondary, and tertiary (e.g., three dimensional) structure of the protein including surfaces for binding and interacting with various molecules is well known to be essential to the biological function which the protein exhibits. A protein can also undergo various conformational changes upon binding a molecule at a particular binding site. Monomeric methionine does not have the same type of complex three-dimensional structure, and would not be expected to stimulate growth of neutrolphil granulocytes. Thus, a person of ordinary skill

[3] See U.S. Patent No. 4,961,926, column 2, lines 41 to 43.
[4] See U.S. Patent No. 4,961,926, column 7, line 67 to column 8, line 14.

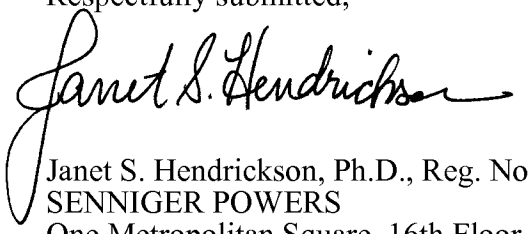
would not have expected methionine by itself to be an effective agent against mucositis based on the Gabrilove disclosure alone or as combined with the Campbell disclosure.

It is respectfully submitted that the Office has failed to establish obviousness based on any reference or by evidence of the level of skill in the art or the nature of the problem that is not based upon impermissible hindsight reconstruction. Thus, claims 1, 3-15, 22-28, and 33-37 are patentable over the cited references.

CONCLUSION

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

Respectfully submitted,



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